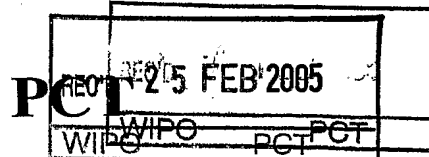


PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:
MARC E. BROWN
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **22 FEB 2005**

FOR FURTHER ACTION
See paragraph 2 below

Applicant's or agent's file reference

38586-339

International application No.

PCT/US04/28162

International filing date (day/month/year)

30 August 2004 (30.08.2004)

Priority date (day/month/year)

29 August 2003 (29.08.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 38/00, 31/56; C12N 5/08 and US Cl.: 424/93.21, 9.1; 435/69.4, 325, 366, 7.2; 514/2, 170; 530/350; 548/241

Applicant

REGENTS OF THE UNIVERSITY OF CALIFORNIA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US
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Chih-Min Kam

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/28162

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/28162

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
- ☐ paid additional fees
 - ☐ paid additional fees under protest
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-12 and 51

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/28162

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1-12 and 51</u>	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>1-12 and 51</u>	YES
	Claims <u>NONE</u>	NO
Industrial applicability (IA)	Claims <u>1-12 and 51</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

1. Claims 1-12 and 51 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method of inducing osteoblastic differentiation of mammalian mesenchymal stem cells or a method of stimulating mammalian cells to express a level of biological marker of osteoblastic differentiation by treating the mammalian cells with at least one oxysterol and at least one bone morphogenic protein, and a medicament for treating bone disorders using at least one oxysterol and at least one bone morphogenic protein.

2. Claims 1-12 and 51 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/28162

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

1. Claims 2, 7 and 51 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 2, 7 and 51 are indefinite for the following reason(s): The claim cites the term "a portion", it is not clear what part of hydroxycholesterol or pregnanolone the portion refers to.